

Drug Therapy in Pregnant and Nursing Women

CATHERINE S. STIKA AND MARILYNN C. FREDERIKSEN

Department of Obstetrics and Gynecology, Northwestern University Medical School, Chicago, Illinois

The pregnant woman is perhaps the last true therapeutic orphan. Because of the ethical, medicolegal, and fetal safety concerns regarding pregnant women, few pharmacokinetic, pharmacodynamic, or clinical trials are conducted during pregnancy. The majority of drugs that are marketed in the United States, therefore, carry the following statement (1) in their labeling:

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. [Zinacef (cefuroxime) labeling; PDR; 2005. p. 1678]

This places the burden squarely on the practitioner to assess the risks and benefits of a particular agent in a given clinical situation. The risk most often considered is the fetal risk of teratogenesis, or drug-induced malformation, irrespective of the gestational age during the pregnancy when therapy is initiated. Pregnant women are more often than not left untreated in an attempt to avoid any perceived fetal risk related to use of a pharmacologic agent, and the effect of untreated maternal disease on either the pregnancy outcome or the offspring is not always considered. Issues of appropriate dosage and frequency of administration are often not evaluated, so that the usual adult dose is prescribed without thought to any changes dictated by physiologic differences between nonpregnant and pregnant women.

There are two compelling reasons for studying drugs and drug therapy during pregnancy. The first

relates to the changing age of reproduction. Pregnancy once was mainly undertaken by healthy, younger women, but the age of reproduction now includes women ranging in age from 10 to approximately 50 years, and with *in vitro* fertilization and egg donation, even older women undertake pregnancy. Moreover, the age of a woman's first pregnancy has been steadily rising in the United States, with an increasing number of first pregnancies occurring after age 30 (2). The expansion of the reproductive age range, coupled with the occurrence of pregnancy later in life, increases the number of women who may require drug therapy for diseases present prior to pregnancy and who may need to continue therapy during pregnancy. Knowledge of drug therapy during pregnancy is needed if these women with underlying diseases are to be optimally treated.

The second reason supporting the need to study drugs during pregnancy relates to the physiologic changes that occur with gestation. To accommodate fetal growth and development, and perhaps provide a measure of safety for the woman, pregnancy alters a woman's underlying physiology. This altered physiology can affect the pharmacokinetics of drugs. The changes may alter peak drug concentration and time to peak drug concentration by affecting drug absorption, may decrease drug binding to plasma proteins and increase drug distribution volume, and may cause variations in either renal and/or hepatic drug clearance. Extrapolation of pharmacokinetic data from drug studies largely conducted in nonpregnant

subjects to pregnant women fails to account for the impact of physiologic changes that occur during pregnancy. This disregard for the changes in maternal physiology may affect drug efficacy and ultimately may impact the overall pregnancy outcome.

These issues have begun to be addressed by the Food and Drug Administration, which has established a Pharmacokinetics in Pregnancy Working Group of the Pregnancy Labeling Task Force, associated with the Center for Drug Evaluation and Research.

PREGNANCY PHYSIOLOGY AND ITS EFFECTS ON PHARMACOKINETICS

Rather than present a list of the many changes in maternal physiology that occur during pregnancy, the focus here is to select those changes that have the greatest potential to alter the absorption, distribution, and elimination of drugs in pregnant women.

Gastrointestinal Changes

The effect of progesterone on smooth muscle activity has long been thought to prolong gastric emptying and gastrointestinal transit time during all of pregnancy. However, most of the early studies were done in women during labor (3, 4). Studies of acetaminophen absorption using real-time ultrasonographic assessment of gastric emptying in nonlaboring women have shown no differences in gastric emptying during the first and third trimesters and in the postpartum period (5, 6). Only in the third trimester of pregnancy are orocecal transit times prolonged. This effect is due to the lower level of pancreatic polypeptide that occurs in the third trimester of pregnancy and results in reduced gastrointestinal motility (5). Pregnant women, however, have a decrease in gastric acid secretion that results in a correspondingly higher gastric pH (7).

The effects of gastrointestinal changes that occur during pregnancy were studied with ampicillin, a drug that is only 40% absorbed orally (8). Women were studied while they were pregnant as well as after pregnancy, thus serving as their own controls. The absolute bioavailability of ampicillin was evaluated by administering ampicillin both orally and intravenously to each woman during pregnancy and again postpartum. Pregnancy did not appear to change the extent of ampicillin absorption or the time to peak drug concentration (t_{max}). However, peak drug levels were found to be lower during pregnancy.

Cardiovascular Effects

The cardiovascular effects that occur during pregnancy include plasma volume expansion, an increase in cardiac output, and changes in regional blood flow. By the sixth to eighth week of pregnancy, plasma volume has expanded and continues to increase until approximately 32 to 34 weeks of pregnancy (9). For a singleton gestation, this increase in plasma volume is 1200–1300 mL, or approximately 40% higher than the plasma volume of nonpregnant women. Plasma volume expansion is even greater for multiple gestations (10). There are also significant increases in extracellular fluid space and total body water that vary somewhat with patient weight. These changes in body fluid spaces are summarized in Table 22.1 (11, 12).

The increase in plasma volume is accompanied by a gradual increase in cardiac output that begins in the first trimester of pregnancy. By 8 weeks' gestation, cardiac output can be as much as 50% greater, and by the third trimester is at least 30–50% greater than in the nonpregnant state (13). Early in pregnancy, an increase in stroke volume accounts for the increased cardiac output. In later pregnancy, the increase in cardiac output is the result of both elevated maternal heart rate and a continued increase in stroke volume (14).

Regional blood flow changes also occur in pregnant women and can affect drug distribution and elimination. Blood flow increases to the uterus, kidneys, skin, and mammary glands, with a compensatory decrease in skeletal muscle blood flow. At full term, blood flow to the uterus represents about 20–25% of cardiac output and renal blood flow is 20% of cardiac output (15). There is increased blood flow to the skin to dissipate the additional heat produced by the fetus (16). Blood

TABLE 22.1 Body Fluid Spaces in Pregnant and Nonpregnant Women^{a,b}

Patient	Weight (kg)	Plasma volume (mL/kg)	ECF space (L/kg)	TBW (L/kg)	Ref.
Nonpregnant		49			9
	<70		0.189	0.516	11
	70–80		0.156	0.415	11
	>80		0.151	0.389	11
Pregnant		67			9
	<70		0.257	0.572	12
	70–80		0.255	0.514	12
	>80		0.240	0.454	12

^a Modified from Frederiksen *et al.* Clin Pharmacol Ther 1986;40:321–8.

^b Abbreviations: ECF, extracellular fluid; TBW, total body water.

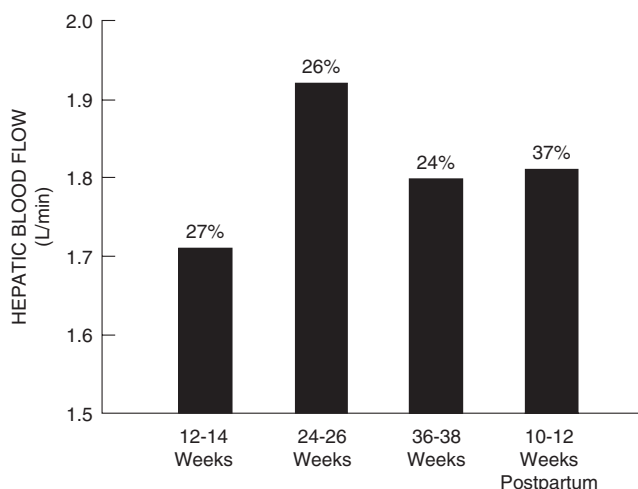


FIGURE 22.1 Hepatic blood flow expressed in L/min (*bars*) and as percentage of cardiac output (*numbers above bars*) during pregnancy and in the postpartum period. Although the absolute value of hepatic blood flow is unchanged, it comprises a significantly lower percentage of cardiac output during pregnancy, compared to postpartum. (Data from Robson SC *et al.* Br J Obstet Gynaecol 1990;97:720–4.)

flow to the mammary glands is increased during pregnancy in preparation for lactation postpartum (17). As shown in Figure 22.1, hepatic blood flow is maintained unchanged during pregnancy but constitutes a lower percentage of cardiac output than in the nonpregnant condition because of the increased proportion of blood flow to the uterus and kidneys (18). As a result of these hemodynamic changes, there is a decreased proportion of cardiac output available to skeletal muscle and other vascular beds.

These multiple physiological changes in pregnant women may affect drug distribution. In some cases, it is possible to correlate pregnancy-associated changes in distribution volume (V_d) with changes in extracellular fluid space (ECF), total body water (TBW), and drug binding to plasma proteins using the following equation, which was developed in Chapter 3:

$$V_d = ECF + f_u(TBW - ECF) \quad (22.1)$$

where f_u is the fraction of unbound drug.

Blood Composition Changes

Plasma albumin concentration decreases during pregnancy (19, 20). The decrease in albumin concentration from 4.2 g/dL in the nonpregnant woman to 3.6 g/dL in the midtrimester of pregnancy (Figure 22.2) has long been attributed to a “dilutional effect” caused by plasma volume expansion. However, a more likely explanation is that this

decrease in plasma albumin concentration represents either a reduction in the rate of albumin synthesis or an increase in the rate of albumin clearance (see Chapter 1, Equation 1.1). Additional support for this explanation is provided by the fact that the plasma concentrations of total protein (19) and α_1 -acid glycoprotein (21), which binds many basic drugs, are relatively unchanged during pregnancy.

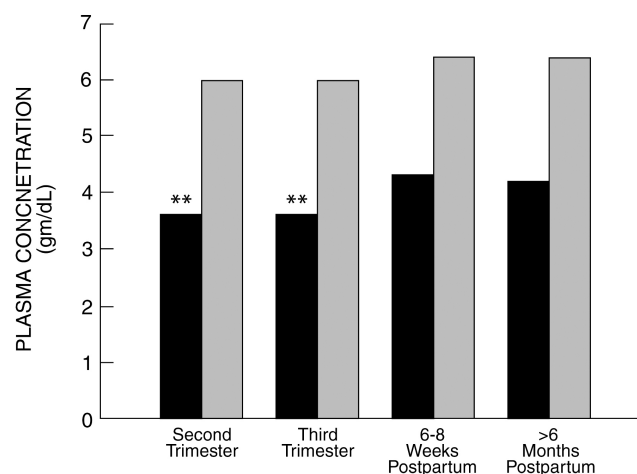


FIGURE 22.2 Albumin (*black bars*) and total protein (*gray bars*) concentrations during the second and third trimesters of pregnancy and in the postpartum period. Albumin concentrations are reduced significantly during pregnancy when compared to postpartum values at >6 months (** = $P < 0.01$). (Data from Frederiksen MC *et al.* Clin Pharmacol Ther 1986;40:321–8.)

The reduction in albumin concentration potentially can alter the binding of drugs commonly bound to serum albumin. In a study of theophylline pharmacokinetics during the second and third trimesters of pregnancy, theophylline protein binding to plasma proteins was reduced to only 11 and 13% of total plasma concentrations, respectively, compared with 28% at 6 months postpartum (20). Although the decrease in the serum concentration of albumin may be thought to account for these differences, a subsequent study showed that the albumin binding sites for theophylline were actually increased during pregnancy, but the binding affinity constant was significantly lower during pregnancy than in the nonpregnant state (22).

Pregnancy is also associated with a partially compensated respiratory alkalosis that may affect the protein binding of some drugs. Respiratory changes in pregnancy include a decrease in arterial partial pressure of carbon dioxide to 30.9 mm Hg, most likely due to the effect of progesterone (23, 24). In compensation, serum bicarbonate decreases, and maternal serum pH increases slightly to 7.44 (23).

Renal Changes

Accompanying the increased blood flow to the kidneys is an increase in glomerular filtration rate (GFR). This increase begins by the sixth week of gestation, gradually rises into the early portion of the third trimester (25), and plateaus or falls slightly until delivery. This increase in GFR is reflected in an increase in inulin and creatinine clearance during pregnancy. Tubular reabsorption processes, however, do not appear to be changed during pregnancy. (26)

For drugs predominantly cleared by the kidney, the increase in GFR will increase drug clearance during pregnancy. Cefuroxime, a cephalosporin predominantly eliminated by the kidneys, has a significantly greater clearance in the midtrimester of pregnancy than during either delivery or the postpartum period (27). Tobramycin clearance mirrors the GFR changes in pregnancy, with the highest clearance and shortest half-life found in the midtrimester, with a decrease in clearance and corresponding longer half-life in the third trimester (28).

Even for a drug primarily eliminated by hepatic metabolism in nonpregnant women, the increase in GFR can significantly affect total drug clearance during pregnancy. For example, the renal clearance of theophylline, a drug largely eliminated by CYP1A2 metabolism, was found to increase during pregnancy so that its total elimination clearance was not

significantly reduced but was maintained at 86% of its value 6 months postpartum (20).

Hepatic Drug-Metabolizing Changes

The activity of hepatic drug-metabolizing enzymes also changes during pregnancy and can affect drug elimination clearance. Pregnancy is an estrogenic state with 100-fold increases in estradiol levels over a woman's nonpregnant baseline (29, 30). Progesterone, the hormone responsible for sustaining gestation, also dramatically rises during pregnancy from luteal levels of 30–40 ng/mL to levels of 100–200 ng/mL (31–33). These changes in estrogen and progesterone, as well as in other placental hormones, can alter hepatic enzymatic activity.

CYP3A4 Substrates

The clearances of drugs metabolized by CYP3A4 have been shown to be consistently increased in multiple studies of pregnant women. Because midazolam is exclusively eliminated by CYP3A4 metabolism (34, 35), midazolam clearance and the serum concentration ratio of 1'-hydroxymidazolam to midazolam are recognized markers of CYP3A4 activity. (36, 37) In pregnant women at term, the clearance of midazolam has been shown to be 2.9-fold greater than in nonpregnant women (38). The metabolic ratio of cortisol, a nonspecific probe of CYP3A4 activity, was increased in pregnant women near term when compared to the same women 1 week and 3 months postpartum (39). The clearance of nifedipine was increased 4-fold in women during the third trimester of pregnancy in comparison to historical controls (40). Methadone, a drug used to treat heroin addiction during pregnancy, also is a CYP3A4 substrate. In a study of methadone pharmacokinetics during pregnancy, methadone clearance doubled in the midtrimester but fell somewhat in the third trimester (41). This change was both statistically and clinically significant because the lower methadone plasma levels will result in symptoms of methadone withdrawal unless methadone dosage is increased during pregnancy. In a study of the extended release formulation of metronidazole, which is primarily metabolized by CYP3A4, the total oral clearance in pregnant women during the second and early third trimester was 27% greater than in nonpregnant women (42). The mean maximum concentration of metronidazole was approximately 25% lower in pregnancy and the difference in areas under the concentration curves (AUCs) in pregnant versus nonpregnant women approached significance.

The critical stimulus for CYP3A4 induction in pregnancy has not been identified. However, both estradiol and estrone, as well as the natural progestins, including progesterone, pregnenolone, 17-hydroxyprogesterone, and 5 β -pregnane-3,20-dione, have been shown to activate the human orphan nuclear pregnane X receptor (PXR). As described in Chapters 11 and 15, PXR forms a heterodimer complex with the 9-*cis*-retinoic acid receptor (RXR). This hPXR/RXR complex then binds to the promoter region of the *CYP3A4* gene, also called the rifampicin/dexamethasone response element, and serves as a key transcriptional regulator (43, 44).

CYP1A2 Substrates

The elimination clearance of caffeine, a CYP1A2 substrate, was shown to decrease by a factor of two by midgestation and by a factor of three by the third trimester compared to the postpartum period (45). Although the intrinsic hepatic clearance of theophylline was reduced during pregnancy (Figure 22.3), there was substantially less change in its hepatic clearance because of the pregnancy-associated decrease in theophylline binding to plasma proteins (20).

As a result of the offsetting changes in renal and hepatic clearance referred to previously, the total elimination clearance of theophylline was unchanged in the third trimester of pregnancy

CYP2D6 Substrates

Wadelius *et al.* (46) found that CYP2D6 activity, known to be genetically determined, was actually increased during pregnancy in individuals who were homozygous and heterozygous extensive metabolizers. The activity of this enzyme, however, was decreased in homozygous poor metabolizers.

CYP2C9 Substrates

The hepatic clearance of phenytoin, a restrictively eliminated drug that is predominantly a CYP2C9 substrate, increases during pregnancy, resulting in correspondingly lower total plasma concentrations (47). This is in large part a reflection of the decrease in protein binding that is well documented for phenytoin, as free plasma concentrations of this drug have been shown to remain relatively constant until late in pregnancy when the intrinsic clearance of this drug does increase (48, 49).

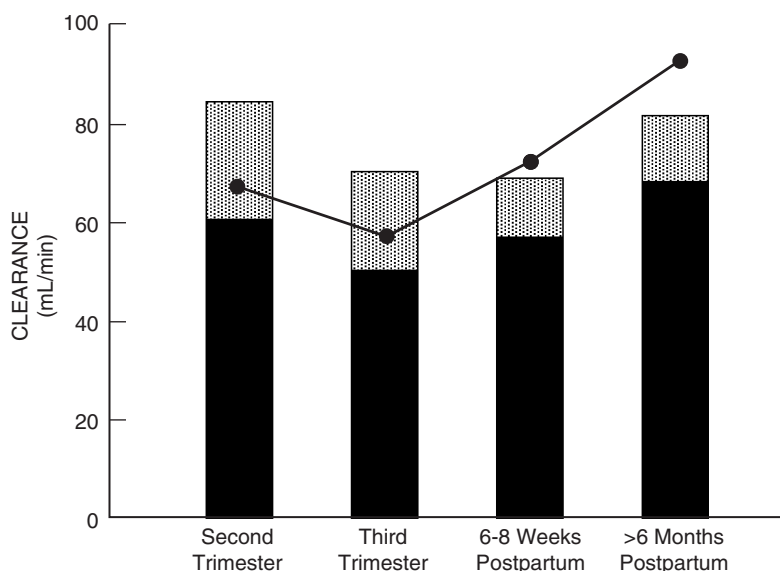


FIGURE 22.3 Theophylline clearance measured during the second and third trimesters of pregnancy and in the postpartum period. During pregnancy, the substantial drop in the intrinsic hepatic clearance (●) of this CYP1A2 substrate is attenuated by decreased theophylline binding to plasma proteins and increased glomerular filtration rate, so that overall elimination clearance, consisting of the sum of hepatic clearance (solid bars) and renal clearance (stippled bars), is relatively unaffected. (Data from Frederiksen MC *et al.* Clin Pharmacol Ther 1986; 40:321–8.)

CYP2C19 Substrates

The metabolism of proguanil, an antimalarial drug, to its active metabolite, cycloguanil, is dependent on CYP2C19 activity. The metabolic ratio of proguanil to cycloguanil has been shown to increase by approximately 60% during pregnancy (50). In a population-based study, CYP2C19 dependent clearance decreased by 50% (51).

NAT2 Substrates

Using caffeine to examine the changes in hepatic enzymatic activity during pregnancy, Bologna *et al.* (52) studied both pregnant and nonpregnant epileptic women and showed that the activity of *N*-acetyltransferase (NAT) was decreased during pregnancy. Tsutsumi *et al.* (53) also used caffeine to show that the activity of *N*-acetyltransferase-2 was decreased in normal healthy women during pregnancy.

Glucuronidation

Lamotrigine, an anticonvulsant and mood-stabilizing drug, is metabolized by glucuronidation. Lamotrigine clearance has been studied by Tran *et al.* (54) during pregnancy and shown to increase by greater than 50%, necessitating dose adjustment. The clearance of lamotrigine returns rapidly to stable nonpregnant levels after delivery so that dose reductions are required in the first 2 weeks postpartum (54, 55).

Betamethasone is glucuronidated by the liver and its clearance has been shown to be higher in pregnant than in nonpregnant women (56). In twin gestations, betamethasone has been shown to have a higher clearance and correspondingly shorter half-life than in singleton gestations (56). This is thought to be caused by increased metabolism of betamethasone by the additional fetoplacental unit present in twin pregnancies. The shorter half-life and higher clearance may explain the decreased efficacy of betamethasone in reducing the incidence of respiratory distress syndrome in twin gestations.

Peripartum Changes

The physiologic changes which begin early in gestation are most pronounced in the third trimester of pregnancy. Further physiologic changes occur during labor and delivery. There is an even further increase in cardiac output, blood flow to muscle mass decreases, and there is a cessation of gastrointestinal activity (57). The onset of uterine contractions decreases placental blood flow and drug distribution to the fetus. During the intrapartum period there also may be a change

in the pharmacodynamics of drugs, but this is largely unstudied.

Drugs are very commonly studied during the intrapartum period, probably for no other reason than the amount of drug distributed to the fetus can be estimated from cord blood obtained at delivery. However, the pharmacokinetics of drugs given during this period have been shown to be different from their pharmacokinetics during the antepartum period. An intrapartum study of cefuroxime showed that clearance was lower than during pregnancy but higher than in the remote postpartum period (58). Morphine clearance has been shown to be markedly increased during labor, resulting in a shortening of its elimination half-life that reduces the dosing interval required for adequate pain relief during labor (59).

Postpartum Changes

In the early postpartum period, maternal pregnancy physiologic changes are sustained, with an elevated cardiac output, decreased plasma albumin concentration, and increased GFR (60, 61). The cardiovascular changes of pregnancy are sustained as long as 12 weeks after delivery (62). However, maternal hepatic enzymatic activity may either rapidly reverse within 24 hours of delivery or return to normal gradually during the first months after delivery (55, 63).

The physiology of the postpartum period seems to have great interindividual variability, since pharmacokinetic studies during this period show greater variability among postpartum women compared to studies conducted in either nonpregnant women or normal volunteers. As shown in Figure 22.4, a study of clindamycin pharmacokinetics in five postpartum women demonstrated that there was a 15-fold variation in peak drug concentrations and that $t_{\max}$ varied from 1 to 6 hours after oral administration (64). Similarly, a study of gentamicin in the postpartum period showed distribution volume estimates that varied from 0.1 to 0.5 L/kg, as compared with distribution volume estimates from studies in nonpregnant volunteers that ranged from only 0.2 to 0.3 L/kg (65).

PHARMACOKINETIC STUDIES DURING PREGNANCY

Results of Selected Pharmacokinetic Studies in Pregnant Women

Although an exhaustive survey of pharmacokinetic studies is not possible, the purpose here is to present illustrative studies that best demonstrate the effects of

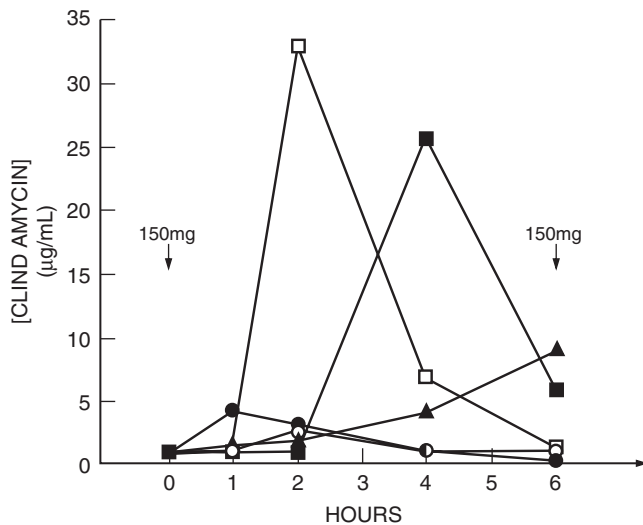


FIGURE 22.4 Plasma concentrations of clindamycin measured in five postpartum women over a 6-hour period after oral administration of a 150-mg dose. (Reproduced with permission from Steen B, Rane A. *Br J Clin Pharmacol* 1982;13:661-4.)

maternal physiologic changes on the pharmacokinetics of drugs and potentially dosing and drug efficacy.

Ampicillin

The pharmacokinetics of both intravenously and orally administered ampicillin were studied serially in 26 women who served as their own controls (8). The study combined data from women whose pregnancies ranged from 13 to 33 weeks' gestation, which blurred assessment of the effects of the progression of changes in maternal physiology that occurs during the second and third trimester of pregnancy. Perhaps because both intravenous and oral doses need to be administered, ampicillin is the only medication for which absolute bioavailability has been examined during pregnancy. No difference in the extent of ampicillin absorption or in time to peak drug concentrations was seen between pregnant and nonpregnant women, but peak levels in pregnant women were lower than those in nonpregnant women. Although this study demonstrated an absolute increase in the distribution volume of ampicillin, it did not include an analysis of the effect of the change in maternal weight on the volume of distribution. Both renal and total elimination clearance (CL) of ampicillin increased by approximately 50% during pregnancy and resulted in correspondingly lower plasma concentrations. Another study of ampicillin pharmacokinetics in the third trimester of pregnancy showed an increase in the steady-state volume of distribution on a liter/kilogram basis (66).

Unfortunately, for this study, the authors used male controls as an historic reference population.

Caffeine

The pharmacokinetics of caffeine also were studied serially during and after pregnancy (45). Although only oral doses were administered, V_d/F showed no change when calculated on a liter/kilogram basis to take into account the change in weight during and after pregnancy. On the other hand, CL/F was decreased by a factor of two by midgestation and by a factor of three in the third trimester compared to the postpartum period (45).

Theophylline

The pharmacokinetics of intravenously administered theophylline pharmacokinetics have been studied serially in women during and after pregnancy (20). As described previously, theophylline binding to plasma proteins was reduced during the second and third trimesters of pregnancy to 11 and 13% of total plasma concentrations, respectively, compared with 28% at 6 months postpartum. This appears to reflect the fact that the albumin binding affinity constant for theophylline is significantly lower during pregnancy than in the nonpregnant state, even though there is an increased number of albumin binding sites (22). The steady-state distribution volume of theophylline was increased during the second and third trimesters of pregnancy. As shown in Table 22.2, the increases were similar to what was predicted from Equation 22.1 using measured values for protein binding and the estimates of extracellular fluid volume and total body water shown in Table 22.1.

TABLE 22.2 Comparison of Expected with Measured Values of Theophylline Distribution Volume^a

Patient	$V_{(dss)}^b$	
	Expected (L)	Measured (L)
Pregnant		
24-26 weeks	32.0 ± 2.0	30.3 ± 6.6
36-38 weeks	37.9 ± 1.9	36.8 ± 4.2
Postpartum		
6-8 weeks	28.0 ± 1.1	28.4 ± 3.0
>6 months	26.9 ± 2.3	30.7 ± 4.4

^a Data from Frederiksen *et al.* *Clin Pharmacol Ther* 1986;40:321-8.

^b Mean values for five women ± SD.

Renal clearance of theophylline paralleled the pregnancy-associated increase in creatinine clearance and accounted for 30 and 28% of total theophylline elimination in the second and third trimesters, respectively, compared to only 16% at 6 months postpartum. As was shown in Figure 22.3, the intrinsic clearance of theophylline was reduced substantially during pregnancy. Hepatic clearance showed substantially less change because of the pregnancy-associated decrease in theophylline binding to plasma proteins. As a result of the offsetting changes in renal and hepatic clearance, total elimination clearance of theophylline in the third trimester of pregnancy averaged 86% of its value at 6 months postpartum. Although this reduction in elimination clearance was not statistically significant, it combined with the increase in theophylline distribution volume to significantly increase theophylline elimination half-life from an average of 4.4 hours in the nonpregnant state (assessed 6 months postpartum) to 6.5 hours in the third trimester of pregnancy.

Cefuroxime

The pharmacokinetics of intravenously administered cefuroxime were studied serially in seven women during pregnancy, at delivery, and in the remote postpartum period (27). Distribution volume ($V_{d(\text{extrap})}$) during pregnancy and at delivery approximated the expected ECF volumes shown in Table 22.1. However, the difference in these volumes and the postpartum value was not statistically significant and there was no change in the weight-normalized distribution volumes. On the other hand, cefuroxime is largely eliminated by renal excretion, and renal clearance was significantly greater during pregnancy than that measured either at delivery or in nonpregnant women. As a result, plasma cefuroxime concentrations resulting from a 750-mg dose were significantly lower during pregnancy.

Methadone

The pharmacokinetics of orally administered methadone were studied serially in nine women at 20–24 weeks and 35–40 weeks of pregnancy and at 1–4 weeks and 8–9 weeks postpartum (41). There was no significant change in methadone binding to plasma proteins during pregnancy. Renal methadone clearance during pregnancy was approximately twice its value in the postpartum periods. However, renal clearance contributed only minimally to total methadone clearance and this change did not reach statistical

significance. On the other hand, estimates of CL/F during pregnancy were also doubled and this change was both statistically and clinically significant, resulting in a corresponding lowering of methadone plasma levels and symptoms of methadone withdrawal in some women near the end of gestation. Because the clearance of other CYP3A4 substrates is increased during pregnancy, it was concluded in this study that increased metabolic clearance rather than decreased bioavailability was responsible for the decrease in CL/F .

Anticonvulsants

The total plasma concentrations of most anticonvulsant drugs have been shown to decrease during pregnancy. This is in large part a reflection of the decrease in protein binding that is well documented for phenytoin (47, 48), carbamazepine (48), and phenobarbital (49). However, these drugs are restrictively eliminated and unbound concentrations of carbamazepine (38, 67) and phenobarbital (49) remain unchanged during pregnancy, reflecting the fact that their intrinsic clearance is unchanged. As is the case for patients with impaired renal function (see Chapter 5), dosage of phenytoin and these other anticonvulsants should not be increased in pregnant women based solely on decreases in total plasma concentration. On the other hand, Tomson *et al.* (48) monitored phenytoin plasma levels serially in 36 women during pregnancy and in the nonpregnant state. Intrinsic clearance was increased only during the third trimester of pregnancy, resulting in unbound plasma concentrations that averaged 16% lower than in the nonpregnant state (Figure 22.5), and this may warrant increasing phenytoin doses for some women late in pregnancy.

Other Drugs

The clearance of a number of other drugs that are eliminated primarily by renal excretion has also been shown to increase during pregnancy. For example, the pharmacokinetics of subcutaneously administered enoxaprin, a low molecular weight heparin, were studied serially in 13 women at 12–15 weeks and 30–33 weeks of gestation and 6–8 weeks postpartum (68). Compared to postpartum values, elimination clearance was increased by approximately 50% in the first gestational study period but was not significantly increased in the later period. In another study, the clearance of tobramycin was shown to peak in the midtrimester and decrease during the third trimester (28).

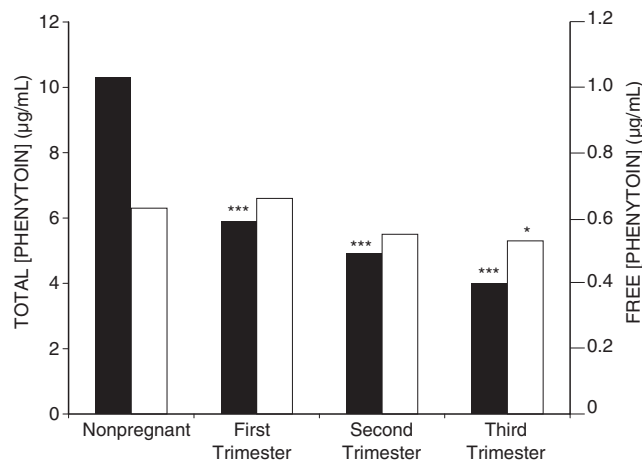


FIGURE 22.5 Total (black bars) and free (white bars) plasma concentrations of phenytoin in nonpregnant and pregnant women (* = $P < 0.05$, *** = $P < 0.001$) (Data from Tomson T *et al.* *Epilepsia* 1994;35:122–30.)

Plasma concentrations of orally administered nifedipine, another CYP3A4 substrate, have been reported to be decreased in 15 women with pregnancy-induced hypertension who were studied during the third trimester of pregnancy but not subsequently postpartum (69). Estimates of CL/F averaged 2.0 L/hr/kg, compared to a value of 0.49 L/hr/kg that was reported in a study of nonpregnant volunteers. Another study of nifedipine pharmacokinetics in eight patients with preeclampsia indicated that CL/F remains elevated in the immediate postpartum period, averaging 3.3 L/hr/kg in this clinical setting (70).

First-pass conversion of a prodrug to an active drug has been studied in pregnancy with the drug valacyclovir (71). Orally administered valacyclovir produced three times higher plasma levels of acyclovir than when acyclovir was administered orally. However, the levels achieved with valacyclovir were somewhat lower than the reported levels in normal volunteers. On the other hand, acyclovir pharmacokinetics were, overall, similar to what has been reported in nonpregnant women.

Guidelines for the Conduct of Drug Studies in Pregnant Women

Studying drugs in pregnancy requires special considerations, and guiding principles for these studies were formally published by the Pharmacokinetics in Pregnancy Working Group of the Pregnancy Labeling Task Force in the *Guidance for Industry — Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling*, in October, 2004 (72).

Although abstinence from the use of pharmacologic agents is held forth as the ideal during pregnancy, studies have shown that most pregnant women use either prescribed or over-the-counter drugs during pregnancy (73, 74). Ethically, drug studies in pregnancy cannot be done in normal pregnant “volunteers,” but only in women who require a drug for a clinical reason. For this reason, study design for these trials must include the ethical argument that the woman would be using the particular agent during pregnancy to treat a medical condition. For FDA approval of drugs specific to pregnancy, such as a tocolytic agents, oxytocic agents, and a drug to treat preeclampsia, studies must be done during pregnancy. However, drugs commonly used by women of childbearing potential, such as antidepressants, asthma medications, antihypertensive agents, and antihistamines, also can be justifiably studied during pregnancy. Drugs can be studied not only when given for maternal indications (e.g., hypertension or asthma), but also when given for fetal indications (e.g., fetal supraventricular tachycardia).

Some subpopulations of pregnant women, however, often have altered physiology that may affect pharmacokinetics. Therefore, to separate the effects of the specific pathophysiology of the subpopulation on the pharmacokinetics of the drug from those resulting from pregnancy-related changes in general, studies in these women should be designed so that maximal information is obtained. As a first step, population pharmacokinetic techniques can serve as a screening tool to establish the need for further intensive pharmacokinetic studies. For drugs that are chronically administered, these intensive studies should be conducted serially during the second and third trimesters of pregnancy and in the postpartum period, so that each woman serves as her own control. Ideally, both an early and a remote postpartum evaluation should be included. However, drugs used only during the peripartum period need only be studied at that time. Studies should incorporate *in vitro* measurements of drug binding to plasma proteins, and use established tracer substances or concurrent noninvasive measures of physiology as reference markers. For bioavailability evaluations, the stable isotope method described in Chapter 4 would decrease the number of studies necessary and decrease the biologic variation between studies. Caffeine has been used as a probe to assess the effects of pregnancy on drug metabolism and has the advantage over the “cocktail” approaches described in Chapter 7 in that only a single drug is needed to simultaneously assess a number of metabolic pathways (Figure 22.6).

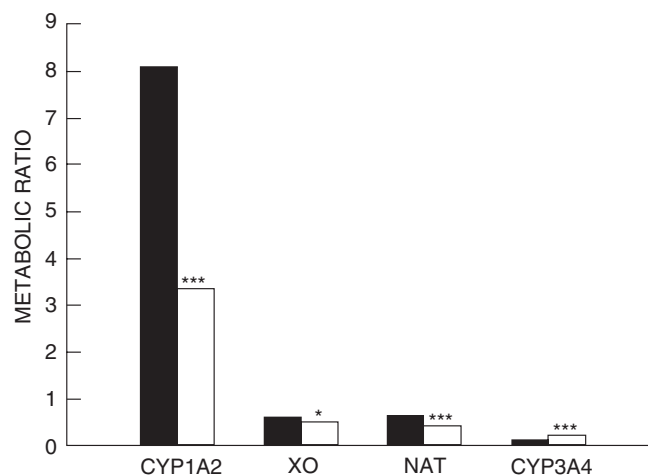


FIGURE 22.6 Paired comparisons of measured ratios of caffeine metabolites to parent drug in nonpregnant (solid bars) and pregnant (open bars) women. Comparisons were made of the metabolic activities of CYP1A2, xanthine oxidase (XO), *N*-acetyltransferase (NAT), and CYP3A4 (* = $P < 0.05$, *** = $P < 0.005$). (Data from Bologna M *et al.* J Pharmacol Exp Ther 1991;257:735–40.

PLACENTAL TRANSFER OF DRUGS

The placenta was long thought to be a barrier to drugs and chemicals administered to the mother. However, the thalidomide tragedy, reported independently by McBride (75) and Lenz (76), showed that the placenta was capable of transferring drugs ingested by the mother to the fetus, with the potential for great harm. On the other hand, placental transfer of drugs administered to the mother has been used to treat fetal arrhythmias, congestive heart failure, and other conditions (77).

The placenta develops from a portion of the zygote and thus has the same genetic endowment as the developing fetus (78). The embryonic/fetal component consists of trophoblastic-derived chorionic villi, which invade the maternal endometrium and are exposed directly to maternal blood in lake-like structures called lacunae. These villi create the large surface area necessary for maternal–fetal transfer in what becomes the intervillous space of the placenta. Here the maternal blood pressure supplies pulsatile blood flow in jetlike streams from the spiral arteries of the endometrium, to bathe the chorionic villi and allow for transfer of gases, nutrients, and metabolic products. Biologically, the human placenta is classified as a hemochorial placenta because maternal blood is in direct contact with the fetal chorionic membrane. It is this membrane that determines what is transferred to the fetus.

For the most part, drugs and other substances given to the mother will be transferred to the fetus. Drugs cross the placenta largely by simple diffusion.

Factors affecting drug transfer are similar to those affecting transfer across other biological membranes and include the molecular mass, lipid solubility, and degree of ionization of the compound. Generally, drugs and chemicals with a molecular mass of less than 600 Da traverse the placenta readily, while drugs with a molecular mass larger than 1000 Da transfer less readily, if at all. Compounds that are uncharged and more lipid soluble are also more readily transferred.

Recently, P-glycoprotein (P-gp) has been shown to play a critical role in the active transport of a large number of maternally administered drugs back into maternal circulation and away from the fetus. As described in Chapter 14, P-gp is a large, 140–170-kDa transmembrane phospho-glycoprotein whose role as an energy-dependent efflux transporter was first elucidated in the investigation of cellular multidrug resistance. Coded for by the *MDR1* gene, P-gp belongs to a superfamily of ATP-binding cassette transporters that are present in all organisms, from bacteria to humans (79–81). Actively excreting absorbed molecules from the cytoplasm, the evolutionary job of P-gp has been to reduce exposure to xenobiotics, or foreign, natural toxins (82, 83). Numerous seemingly structurally unrelated drugs are substrates for this transporter. In general, these compounds can be categorized as hydrophobic, often planar aromatic molecules that are neutral or positively charged at physiological pH.

In humans, P-gp is expressed on trophoblastic cells throughout pregnancy (82, 84–86). It has been located on apical surfaces of endodermal cells of the mouse yolk sac (87), in the vesicles of the brush border membrane of the human syncytiotrophoblast that directly faces maternal blood, but not within maternal vascular endothelium (83, 84, 86–95). Actively transporting molecules in a basolateral-to-apical direction, the role of P-gp within the placenta is similar to its function at other sites: it extrudes drugs from the placenta back into maternal circulation, thereby protecting the developing fetus from potential toxic factors within the maternal circulation (95).

In genetically altered *mdr1a/b* (–/–) knockout mice without P-gp, both transplacental transport of P-gp substrates and the incidence of fetal malformations increase (93). Transplacental transport of the P-gp substrates, digoxin, saquinavir and paclitaxel, was increased 2.4-, 7-, and 16-fold, respectively, in the knockout mice compared to transport in the wild-type animals. In another murine study, *mdr1a/b* (–/–) fetuses were susceptible to cleft palate malformation induced by prenatal exposure to a photoisomer of avermectin B1a, whereas their wild-type littermates were protected from the teratogen (87).

An active transport mechanism has long been suspected to account for the placental barrier that causes maternal and fetal concentrations for many drugs to differ (96, 97). Studies of maternal–fetal transport of medications used during pregnancy in HIV-positive women have shown variable penetration into the fetus (98, 99). Whereas the maternal–fetal drug ratios for zidovudine, lamivudine, and nevirapine (approximately 0.85, 1.0, and 0.9, respectively) demonstrate good fetal penetration, most protease inhibitors, nelfinavir, ritonavir, saquinavir, and lopinavir, are known P-gp substrates and do not cross the placenta in detectable levels (98).

Several studies have examined the interaction between selective serotonin reuptake inhibitors (SSRIs) and P-gp and have shown that not all members of this class of drugs are P-gp substrates. Concentrations of paroxetine and venlafaxine, but not fluoxetine, were significantly increased in the brains of *mdr1a/b* (–/–) knockout mice compared to concentrations in the wild-type mice.(100) In cell culture studies, sertraline, its metabolite desmethylsertraline, and paroxetine were shown to be potent inhibitors of P-gp; however, citalopram and venlafaxine were only weak inhibitors (101, 102).

There are factors that affect the transfer of drugs and chemicals that are unique to the placenta. The placenta has a pore system that allows for bulk water flow across the placenta and can be responsible for small drugs and chemicals crossing the membrane by solvent drag. Within the placenta, there is also a process of endocytosis that is capable of transferring large immunoglobulins to the fetus. Placental tissue has a full complement of cytochrome enzymes capable of metabolizing drugs and chemicals, and some of these metabolites may then transfer more readily to the fetus than the parent drugs do. The permeability and diffusion properties of the placenta may increase as the placenta matures due to a decrease in thickness of the trophoblastic epithelium forming the chorionic membrane.

One of the factors affecting drug transfer to the fetus is the amount of drug delivered to the intervillous space by utero-placental blood flow. Blood flow to the uterus and placenta increases during pregnancy, from 50 mL/min at 10 weeks' gestation to 500–600 mL/min at term (78). Maternal blood flow to the uterus is also influenced by posture, diseases affecting maternal vasculature (such as hypertension and diabetes), placental size, and uterine contractions. For example, maternal cardiac output and utero-placental blood flow are reduced in the supine position and placental perfusion virtually ceases during a contraction. Placentas that are small for gestational age, or those with

diffuse calcifications, are less efficient at transferring any maternal compounds to the fetus. Diseases (such as diabetes, which can thicken the chorionic membrane), may also potentially affect diffusion of drugs into the fetal circulation.

TERATOGENESIS

During the 38 weeks that comprise human gestation, the human conceptus develops from a one-cell zygote to the fully developed newborn infant. This complicated process has a high degree of wastage, with approximately 70% of conceptions lost prior to implantation, 20% lost from spontaneous abortion, and 15% born prematurely. Major congenital abnormalities that are recognized at birth occur in approximately 2 to 3 infants per 100. Minor anomalies occur in another 7 to 14 infants per 100. Major birth defects cause 20% of infant mortality and are responsible for the majority of childhood hospitalizations.

From the patient's perspective, a birth defect may be any abnormality of the infant found at birth. This may include birth injuries, such as a cephalohematoma or a brachial plexus injury. However, birth defects are usually considered to be structural defects of the newborn. Structural defects have been broken down into four major categories: a *malformation*, which is a structural defect caused by an intrinsic problem in embryologic differentiation and/or development; a *disruption*, which is an alteration in shape or structure of a normally differentiated part, such as a limb amputation from an amniotic band or a vascular event; a *deformation*, which is an alteration in the shape or structure of a normally differentiated part, such as a Potter's facies or metatarsus adductus, that is often due to a mechanical constraint; and a *dysplasia*, which is a primary defect in cellular organization into tissues (103). A *teratogen* is a chemical substance that can induce a malformation during development. An expansion of the definition includes an adverse effect on the developing fetus either in causing a structural abnormality or in altering organ function. This should be distinguished from a *mutagen*, which causes a genetic mutation whose effects cannot be seen for at least a generation.

Underlying causes of birth defects are shown in Table 22.3. It should be appreciated that approximately 90% of birth defects have a genetic component. Birth defects caused by drugs represent the one group of anomalies that can potentially be prevented. However, it is a small list of drugs that have been proved to cause human anomalies (Table 22.4). Potential effects of drugs on the developing fetus

TABLE 22.3 Human Reproductive Risk

Cause of anomalies	Percentage of total anomalies
Chromosomal	5
Single gene	20
Polygenic/multifactorial	65
Environmental	10
Irradiation	<1
Maternal disease	1–2
Infection	2–3
Drugs and chemicals	4–5

include altered structural development during the first trimester, producing a dysmorphic infant; altered fetal growth during the second and third trimester of pregnancy; and altered function of organ systems.

TABLE 22.4 Known Human Teratogens

Agent	Teratogenic effect
Carbamazepine	Facial dysmorphogenesis, neural tube defect
Phenytoin	Facial dysmorphogenesis, mental retardation, growth retardation, distal digital hypoplasia
Valproate	Lumbosacral spina bifida, facial dysmorphogenesis
Trimethadione	Facial dysmorphogenesis, intrauterine growth retardation, intrauterine fetal demise, neonatal demise
Coumadin	Nasal hypoplasia, epiphyseal stippling, optic atrophy
Alcohol	Facial dysmorphogenesis, growth retardation, mental retardation
Diethylstilbestrol	Vaginal adenosis, uterine anomalies, vaginal carcinogenesis
Androgens	Masculinization of the female genitalia
Methyl mercury	Growth retardation, severe mental retardation
ACE inhibitors ^a	Oligohydramnios, potential lung hypoplasia, postnatal renal failure
Folic acid antagonists (aminopterin, methotrexate)	Abortion, intrauterine growth retardation, microcephaly, hypoplasia of frontal bones
Thalidomide	Phocomelia
Isotretinoin	CNS anomalies, including optic nerve abnormalities, anomalies, cardiovascular malformations, thymic abnormalities
Inorganic iodides	Fetal goiter
Tetracycline	Bone deposits, teeth discoloration
Lithium	Ebstein's anomaly

^aACE, Angiotensin-converting enzyme.

Principles of Teratology

The principles of teratology have been articulated by Wilson (104). The first principle is that teratogens act with specificity. A teratogen produces a specific abnormality or constellation of abnormalities. For example, thalidomide produces phocomelia, and valproic acid produces neural tube defects. This specificity also applies to species, because drug effects may be seen in one species and not in another. The best example is cortisol, which produces cleft palate in mice but not in humans.

The next principle is that teratogens demonstrate a dose-effect relationship. Given to the mother at a specific time during gestation, low doses can produce no effect, intermediate doses can produce the characteristic pattern of malformation, and higher doses will be lethal to the embryo. Dose-effect curves for most teratogens are steep, changing from minimal to maximal effect by dose doubling. Increasing the dose beyond that found to be lethal to the embryo will eventually lead to maternal death. This is used as an endpoint in animal teratogenicity studies.

The third principle is that teratogens must reach the developing conceptus in sufficient amounts to cause their effects. The extent of fetal exposure to drugs and other xenobiotics is determined not only by maternal dose, route of elimination, and placental transfer, but also by fetal elimination mechanisms. Because the fetal liver is interposed between the umbilical vein and systemic circulation, drugs transferred across the placenta are subject to fetal first-pass metabolism (77). This protective mechanism is compromised by ductus venosus shunting, which enables 30–70% of umbilical venous blood flow to bypass the liver. After drugs reach the fetal system circulation, hepatic metabolism constitutes the primary elimination mechanism and renal excretion is relatively ineffective because the fetal kidney is immature and fetal urine passing into the amniotic fluid is swallowed by the fetus. CYP3A7 is a fetal-specific enzyme that accounts for about one-third of fetal hepatic cytochrome P450. CYP1A1, CYP2C8, CYP2D6, and CYP3A3/4 have also been identified in fetal liver. These enzymes are not only protective, but their presence in fetal tissues other than liver is also capable of converting drugs into chemically reactive teratogenic intermediates such as phenytoin epoxide (see Scheme 11.11) (105).

The fourth principle is that the effect that a teratogenic agent has on a developing fetus depends upon the stage during development when the fetus is exposed. From conception to implantation there is an all-or-nothing effect, in that the embryo, if exposed to a teratogen, either survives unharmed or dies.

This concept developed from Brent's studies of the effects of radiation on the developing embryo and may or may not apply to fetal exposure to chemicals (106). After implantation, during the process of differentiation and embryogenesis, the embryo is very susceptible to teratogens. However, since teratogens are capable of affecting many organ systems, the pattern of anomalies produced depends on which organ systems are differentiating at the time of teratogenic exposure. A difference of one or two days can result in a slightly different pattern of anomalies. After organogenesis, a teratogen can affect the growth of the embryo by producing growth retardation, or by changing the size or function of a specific organ. Of particular interest is the effect of psychoactive agents, such as cocaine, crack, or antidepressants, on the developing central nervous system during the second and third trimesters of pregnancy, as these drugs can potentially affect the function and behavior of the infant after delivery. Giving a teratogen after the fetus has developed normally has no effect on the development of organs already formed. For example, beginning lithium after cardiac development, or valproic acid after the closure of the neural tube, will not produce either drug's characteristic anomalies.

The fifth principle is that susceptibility to teratogens is influenced by the genotype of the mother and fetus. Animal studies have shown that certain animal strains are more susceptible to the production of malformations when exposed to a teratogen, compared to other animal strains. In humans, the fetus homozygous for the recessive allele associated with decreased epoxide hydrolase activity has an increased risk of developing the full fetal hydantoin syndrome (105). Maternal smoking increases the risk for the development of cleft lip and palate in a fetus carrying the atypical allele for transforming growth factor (107). Single mutant genes or polygenic inheritance may explain why certain fetuses are unusually susceptible to teratogens.

Mechanisms of teratogenesis include genetic interference, gene mutation, chromosomal breakage, interference with cellular function, enzyme inhibition, and altered membrane characteristics. The response of the developing embryo to these insults is failure of cell-cell interaction crucial for development, interference with cell migration, or mechanical cellular disruption. The common endpoint is cell death — teratogenesis causing fewer cells. Most mechanisms of teratogenesis are theoretical, not well understood, and imply a genetic component. One exception is the mechanism of thalidomide teratogenesis. In susceptible species, thalidomide causes oxidative DNA damage. Pretreatment with phenyl-*N-tert*-butylnitron

(PBN), a free radical trapping agent, reduces the occurrence of thalidomide embryopathy, suggesting that the mechanism is free radical-mediated oxidative DNA damage (108).

Measures to Minimize Teratogenic Risk

All new drug applications filed with the Food and Drug Administration include data from developmental and reproductive toxicology (DART) studies. These studies, most of which are conducted in mice, rats, and rabbits, examine the effects of the particular agent on all aspects of reproduction, including oogenesis, spermatogenesis, fertility, and fecundity, as well as effects on litter size, spontaneous resorption, fetal malformation, fetal size, and newborn pup function. All studies are designed with dose escalations and with maternal death as the endpoint. Information from these teratologic experiments with the drug is included in the drug labeling. Most human teratogenic reactions to new drugs have been predicted from animal studies. However, animal data are not always applicable to humans, since most animals have a shorter gestational clock than humans have. Species vary in their susceptibility to teratogens, with some animal models being either more or less susceptible to teratogenesis than humans are. If an agent does not produce an anomaly in animal studies, it does not prove that the agent is innocuous in humans.

Safety of a drug for use in human pregnancy is demonstrated by observational studies after the drug is marketed. Proof of teratogenicity in humans is supported by the following events: a recognizable pattern of anomalies; a higher prevalence of the particular anomaly or anomalies in patients exposed to an agent than in a control population; presence of the agent during the stage of organogenesis of the organ system affected; increased incidence of the anomaly after introduction of the agent; and production of the anomaly in experimental animals by administration of the agent during the appropriate stage of organogenesis. Epidemiologic clues to teratogenesis are often found in case reports of abnormal infants, but these are biased in that an abnormal infant is more likely reported than is a normal infant, and the background rate of malformations is high. Better studies are conducted prospectively with an exposed and unexposed control population found before pregnancy outcome is known. Although population-based large-cohort studies begun prior to pregnancy are considered the best type, they are expensive to conduct and limited to those agents used at the time of the study.

A general approach to reduce the risk of human teratogenesis includes planning for pregnancy. Prior

to conception, women with medical problems should be counseled about medications they chronically use, which ones can safely be continued throughout pregnancy, and which ones should be discontinued. Medications should be evaluated and changed if necessary to decrease teratogenic risk. Plasma level monitoring of unbound concentrations of antiepileptic drugs may be helpful in optimizing seizure control, decreasing the need for multiple-drug therapy, and minimizing dosage and fetal risk. Since more than 50% of pregnancies in the United States are unplanned, all women should be treated as potential antenatal patients and counseled regarding use of any new drug in a potential pregnancy. Therefore, when a woman of childbearing potential develops a new medical problem, counseling for pregnancy should be included in management. In general, the use of agents widely used during pregnancy is preferred to use of newer agents. Just stopping pharmacologic therapy or leaving the issue up to the woman does not help her and may place both the mother and the fetus at risk for adverse pregnancy outcome.

When using a known human teratogen, particular attention should be given to prevention of pregnancy. This includes counseling the patient on the fetal effects of the drug being used and on the use of one or more effective forms of contraception. Therapy should be begun with a normal menstrual period or no more than 2 weeks from a negative pregnancy test. When renewing prescriptions for these drugs, it is necessary to verify again that the patient is not pregnant.

DRUG THERAPY IN NURSING MOTHERS

Transfer of drugs into breast milk is bidirectional, reflecting passive diffusion of unbound drug between plasma and blood, rather than active secretion. Factors that affect the milk concentration include binding to maternal plasma proteins, protein binding in milk, lipid content of milk, and physiochemical factors of the drug (109). As shown in Figure 22.7, drug concentrations in breast milk are usually less than plasma concentrations are and there usually is a fixed ratio between milk and plasma concentrations (110). Concentration-dependent saturation of the plasma protein binding precludes calculation of a fixed milk:plasma ratio for a few drugs (Figure 22.8) (111). However, in the usual case, drug concentrations measured in plasma and breast milk are used to calculate a milk:plasma ratio (M/P), from which the daily drug dose to the infant is estimated as follows:

$$\text{Infant dose/day} = C_{\text{maternal}} \times M/P \times V_{\text{milk}} \quad (22.2)$$

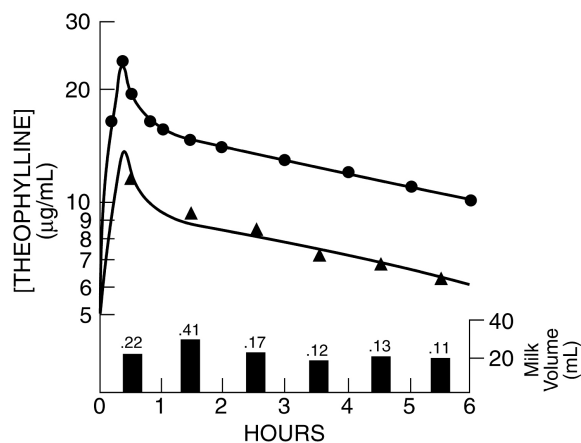


FIGURE 22.7 Kinetic analysis of theophylline plasma (●) and milk (▲) concentrations after intravenous administration of a 3.2- to 5.3-mg/kg aminophylline dose. The lines represent the least-squares fit of the measured concentrations. The interval and volume of each milk collection are shown by the solid bars. The milligram recovery of theophylline in each breast-milk collection is shown by the numbers above the bars. (Reproduced with permission from Stec GP *et al.* Clin Pharmacol Ther 1980;28:404–8.)

where C_{maternal} is the average maternal plasma concentration of drug during nursing and V_{milk} is the volume of maternal milk ingested each day, usually estimated as 150 mL/kg (109). This estimate of infant dose is often reported as a percentage of administered maternal dose.

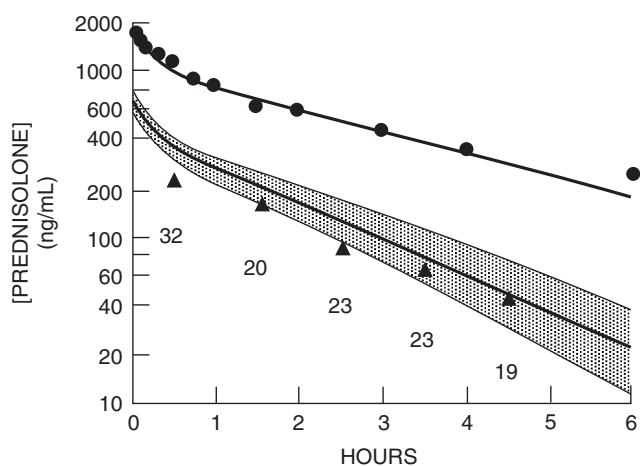


FIGURE 22.8 Kinetic analysis of prednisolone plasma (●) concentrations after intravenous administration of a 50-mg prednisolone dose. The lines represent the least-squares fit of the measured plasma concentrations. Measured milk concentrations (▲) are plotted along with the range (shaded area) of unbound prednisolone plasma concentrations expected if serum transcortin binding capacity is allowed to vary ± 1 SD from its reported mean. The volume (in milliliters) of each breast milk sample is shown by the numbers below the milk concentrations. (Reproduced with permission from Greenberger PA *et al.* Clin Pharmacol Ther 1993;53:324–8.)

TABLE 22.5 Antidepressant Drugs and Breast Feeding

Drug (and metabolite)	Protein binding (%)	M/P ^a	Infant dose ^b (%)	Detectable in infant plasma	Reported infant toxicity	Ref.
NE reuptake inhibitors^a						
Amitriptyline	95	0.5–1.6	1.0	No	No	113, 114
(Nortriptyline)	92	0.7–1.1		No ^c		
(E-10-OH-Nortriptyline)		0.7		Yes ^c		
Doxepin	15–32	1.1–1.7	2.2	Yes	Respiratory depression	115, 116
(N-Desmethyldoxepin)		1.0–1.5		Yes		
Serotonin reuptake inhibitors						
Fluoxetine	>95	0.5–1.5	11	Yes	Colic	117, 118
(Norfluoxetine)	>95	0.6–1.2		Yes		
Sertraline	99	1.9	0.5	Yes	No	119
(N-Desmethylsertraline)		1.6		Yes		
Combined reuptake inhibitors						
Venlafaxine	27	4.1	8	No	No	120
(O-Desmethylvenlafaxine)	3	3.1		Yes		
Atypical antidepressants						
Bupropion	84	5.8	<1	No	No	121
(Hydroxybupropion)		0.1		No		
(Theohydrobupropion)		1.5		No		
Trazodone	93	0.1	<1	Not measured	No	122

^a Abbreviations: M/P = ratio of concentrations in maternal milk and plasma, NE = norepinephrine.

^b Expressed as percentage of maternal dose for combined parent drug and measured metabolites.

^c Both nortriptyline and 10-hydroxynortriptyline concentrations have been measured in the serum of nursing infants whose mothers were treated with nortriptyline (123).

Infant blood levels also can be monitored and levels are usually less than those required for pharmacologic effects. Table 22.5 summarizes representative data for some of the antidepressant drugs that have been used to treat women with postpartum depression. Based on information similar to that in this table, amitriptyline, nortriptyline, and sertraline have been among the antidepressant drugs of choice during breast feeding (112). Regardless of drug choice, an important clinical point, a consequence of the bidirectional transfer of drug between plasma and breast milk, is that infant dosage can be minimized by breast feeding just prior to drug administration, when maternal serum concentration is lowest (110).

Drugs considered safe for pregnancy are usually safe during the lactation period. Drugs contraindicated during lactation include antineoplastics, immune suppressants, ergot alkaloids, gold, iodine, lithium carbonate, radiopharmaceuticals, social drugs of abuse, and certain antibiotics.

REFERENCES

1. Zinacef (cefuroxime) labeling, in Physicians' Desk Reference, 54th ed. Montvale, NJ: Medical Economics; 2005. p. 1678.
2. Births: Preliminary data for 1999. National Vital Statistics Reports. vol 48, number 14. Atlanta, GA: Centers for Disease Control; 2000.
3. Hunt JN, Murray FA. Gastric function in pregnancy. J Obstet Gynaecol Br Emp 1958;65:78–83.
4. Parry E, Shields R, Turnbull AC. Transit time in the small intestine in pregnancy. J Obstet Gynaecol Br Commonw 1970;77:900–1.
5. Chiloire M, Darconza G, Piccioli E, De Carne M, Clemente C, Riezzo G. Gastric emptying and orocecal transit time in pregnancy. J Gastroenterol 2001;36:538–43.
6. Wong CA, Loffredi M, Ganchiff JN, Zhao J, Wang Z, Avram MJ. Gastric emptying of water in term pregnancy. Anesthesiology 2002;96:1395–400.
7. Gryboski WA, Spiro HM. The effect of pregnancy on gastric secretion. N Engl J Med 1976;255:1131–7.
8. Philipson A. Pharmacokinetics of ampicillin during pregnancy. J Infect Dis 1977;136:370–6.
9. Lund CV, Donovan JC. Blood volume during pregnancy: Significance of plasma and red cell volumes. Am J Obstet Gynecol 1967;98:394–403.
10. Hytten F. Blood volume changes in normal pregnancy. Clin Haematol 1985;14:601–12.
11. Petersen VP. Body composition and fluid compartments in normal, obese and underweight human subjects. Acta Med Scand 1957;108:103–11.
12. Plentl AA, Gray MJ. Total body water, sodium space and total exchangeable sodium in normal and

- toxemic pregnant women. *Am J Obstet Gynecol* 1959;78:472-8.
13. Lees MM, Taylor SH, Scott DM, Kerr MR. A study of cardiac output at rest throughout pregnancy. *J Obstet Gynaecol Br Commonw* 1967;74:319-28.
14. Robson SC, Hunter S, Boys RJ, Dunlop W. Serial study of factors influencing changes in cardiac output during human pregnancy. *Am J Physiol* 1989;256:H1060-5.
15. Metcalfe J, Romney SL, Ramsey LH, Burwell CS. Estimation of uterine blood flow in women at term. *J Clin Invest* 1955;34:1632-8.
16. Ginsburg J, Duncan SL. Peripheral blood flow in normal pregnancy. *Cardiovasc Res* 1967;1:132-7.
17. Thoresen M, Wesch J. Doppler measurements of changes in human mammary and uterine blood flow during pregnancy and lactation. *Acta Obstet Gynecol Scand* 1988;67:741-5.
18. Robson SC, Mutch E, Boy RJ, Woodhouse KH. Apparent liver blood flow during pregnancy: A serial study using indocyanine green clearance. *Br J Obstet Gynaecol* 1990;97:720-4.
19. Mendenhall HW. Serum protein concentrations in pregnancy: I. Concentrations in maternal serum. *Am J Obstet Gynecol* 1970;106:388-99.
20. Frederiksen MC, Ruo TI, Chow MJ, Atkinson AJ Jr. Theophylline pharmacokinetics in pregnancy. *Clin Pharmacol Ther* 1986;40:321-8.
21. Wood M, Wood AJJ. Changes in plasma drug binding and α_1 -acid glycoprotein in mother and newborn infant. *Clin Pharmacol Ther* 1981;29:522-6.
22. Connelly RJ, Ruo TI, Frederiksen MC, Atkinson AJ Jr. Characterization of theophylline binding to serum proteins in nonpregnant and pregnant women. *Clin Pharmacol Ther* 1990;47:68-72.
23. Lucius H, Gahlenbeck H, Kleine HO, Fabel H, Bartels H. Respiratory functions, buffer system and electrolyte concentrations of blood during human pregnancy. *Respir Physiol* 1970;9:311-7.
24. Lyons HA, Antonio R. The sensitivity of the respiratory center in pregnancy and after the administration of progesterone. *Trans Assoc Am Physicians* 1959;72:173-80.
25. Davison JM, Hytten FE. Glomerular filtration during and after pregnancy. *J Obstet Gynaecol Br Commonw* 1974;81:588-95.
26. Davison JM, Hytten FE. The effect of pregnancy on the renal handling of glucose. *J Obstet Gynaecol Br Commonw* 1975;82:374-81.
27. Philipson A, Stiernstedt G. Pharmacokinetics of cefuroxime in pregnancy. *Am J Obstet Gynecol* 1982;142:823-8.
28. Bourget P, Fernandez H, Delouis C, Taburet AM. Pharmacokinetics of tobramycin in pregnant women, safety and efficacy of a once-daily dose regimen. *J Clin Pharm Ther* 1991;16:167-76.
29. Buster JE, Abraham GE. The applications of steroid hormone radioimmunoassays to clinical obstetrics. *Obstet Gynecol* 1975;46:489-99.
30. Devroey P, Camus M, Palermo G, Smits J, Van Waesberghe L, Wsanto A *et al.* Placental production of estradiol and progesterone after oocyte donation in patients with primary ovarian failure. *Am J Obstet Gynecol* 1990;162:66-70.
31. Schneider MA, Davies MC, Honour JW. The timing of placental competence in pregnancy after oocyte donation. *Fertil Steril* 1993;59:1059-64.
32. Mishell DR, Thorneycroft IH, Nagata Y, Murata T, Nakamura RM. Serum gonadotropin and steroid patterns in early human gestation. *Am J Obstet Gynecol* 1971;117:631-42.
33. Tulchinsky D, Hobel CJ. Plasma human and chorionic gonadotropin, estrone, estradiol, estriol, progesterone and 17 α -hydroxyprogesterone in human pregnancy. 3. Early normal pregnancy. *Am J Obstet Gynecol* 1973;117:884-93.
34. Kronbach T, Mathys D, Umeno M, Gonzalez FJ, Meyer UA. Oxidation of midazolam and triazolam by human liver cytochrome P450III_{A4}. *Mol Pharmacol* 1989;36:89-96.
35. Gorski JC, Hall SD, Jones DR, VandenBranden M, WRIGHT SA. Regioselective biotransformation of midazolam by members of the human cytochrome P450 3A (CYP 3A) subfamily. *Biochem Pharmacol* 1994;47:1643-53.
36. Thummel KE, Shen DD, Podoll TD, Kunze KL, Trager WF, Hartwell PS *et al.* Use of midazolam as a human cytochrome P450 3A probe: I. *In vitro-in vivo* correlations in liver transplant patients. *J Pharmacol Exper Ther* 1994;271:549-56.
37. Thummel KE, Shen DD, Podoll TD, Kunze KL, Trager WF, Bacchi CE *et al.* Use of midazolam as a human cytochrome P450 3A probe: II. Characterization of inter- and intra-individual hepatic CYP3A variability after liver transplantation. *J Pharmacol Exp Ther* 1994;271:557-66.
38. Kanto J, Sjövall S, Erkkola R, Himberg J-J, Kangas L. Placental transfer and maternal midazolam kinetics. *Clin Pharmacol Ther* 1983;33:786-91.
39. Ohkita C, Goto M. Increased 6-hydroxycortisol excretion in pregnant women: Implication of drug-metabolizing enzyme induction. *DICP* 1990; 24:814-6.
40. Prevost RR, Aki SA, Whybrew WD, Sibai BM. Oral nifedipine pharmacokinetics in pregnancy-induced hypertension. *Pharmacother* 1992;12:174-7.
41. Pond SM, Kreek MJ, Tong TG, Raghunath J, Benowitz NL. Altered methadone pharmacokinetics in methadone-maintained pregnancy women. *J Pharmacol Exp Ther* 1985;233:1-6.
42. Stika CS, Andrews W, Frederiksen MC, Mercer B, Sabai B, Antal E. Steady state pharmacokinetic study of Flagyl[®] ER in pregnant patients during the second to third trimester of pregnancy [abstract]. *Clin Pharmacol Ther* 2004;75:P24.
43. Lehmann JM, McKee DD, Watson MA, Willson TM, Moore JT, Kliewer SA. The human orphan nuclear receptor PXR is activated by compounds that regulate CYP3A4 gene expression and cause drug interactions. *J Clin Invest* 1998;102:1016-23.
44. Goodwin B, Hodgson E, Liddle C. The orphan human pregnane X receptor mediates the transcription activation of CYP3A4 by rifampicin through a distal enhancer module. *Mol Pharmacol* 1999; 56:1329-39.
45. Aldridge A, Bailey J, Neims AH. The disposition of caffeine during and after pregnancy. *Semin Perinatol* 1981;5:310-4.

46. Wadelius M, Darj E, Freene G, Rane A. Induction of CYP2D6 in pregnancy. *Clin Pharmacol Ther* 1997;62:400-7.
47. Tomson T, Lindbom U, Ekqvist B, Sundqvist A. Epilepsy in pregnancy: A prospective study of seizure control in relation to free and total plasma concentrations of carbamazepine and phenytoin. *Epilepsia* 1994;35:122-30.
48. Tomson T, Lindbom U, Ekqvist B, Sundqvist A. Disposition of carbamazepine and phenytoin in pregnancy. *Epilepsia* 1994;35:131-5.
49. Chen SS, Perucca E, Lee JN, Richens A. Serum protein binding and free concentration of phenytoin and phenobarbitone in pregnancy. *Br J Clin Pharmacol* 1982;3:547-52.
50. McGready R, Stepniewska K, Seaton E, Cho T, Cho D, Ginsberg A *et al.* Pregnancy and use of oral contraceptives reduces the biotransformation of proguanil to cycloguanil. *Eur J Clin Pharmacol* 2003;59:553-7.
51. McGready R, Stepniewska K, Edstein MD, Cho T, Gilveray CT, Looareesuwan S *et al.* The pharmacokinetics of atovaquone and proguanil in pregnant women with acute falciparum malaria. *Eur J Clin Pharmacol* 2003;59:545-52.
52. Bologna M, Tang B, Klein J, Tesoro A, Koren G. Pregnancy-induced changes in drug metabolism in epileptic women. *J Pharmacol Exp Ther* 1991; 257:735-40.
53. Tsutsumi K, Kotegawa T, Matsuki S, Tanaka Y, Ishii Y, Kodama Y, Kuranari M, Miyakawa I, Nakano S. The effect of pregnancy on cytochrome P4501A2, xanthine oxidase, and N-acetyltransferase activities in humans. *Clin Pharmacol Ther* 2001;70:121-5.
54. Tran TA, Leppik IE, Blesi K, Sathanandan ST, Rummel R. Lamotrigine clearance during pregnancy. *Neurology* 2002;59:251-5.
55. Ohman I, Vitois S, Tomson T. Lamotrigine in pregnancy: Pharmacokinetics during delivery, in the neonate, and during lactation. *Epilepsia* 2000; 41:709-13.
56. Ballabh P, Lo ES, Kumari J, Cooper TB, Zervoudakis I, Auld PAM, Krauss AN. Pharmacokinetics of betamethasone in twin and singleton pregnancy. *Clin Pharmacol Ther* 2002;71:39-45.
57. Lees MM, Scott DH, Kerr MG. Haemodynamic changes associated with labour. *J Obstet Gynaecol Br Commonw* 1970;77:29-36.
58. Philipson A, Stierstedt G. Pharmacokinetics of cefuroxime in pregnancy. *Am J Obstet Gynecol* 1982;142:823-8.
59. Gerdin E, Salmonson T, Lindberg B, Rane A. Maternal kinetics of morphine during labour. *J Perinat Med* 1990;18:479-87.
60. Ueland K, Metcalfe J. Circulatory changes in pregnancy. *Clin Obstet Gynecol* 1975;18:41-50.
61. Sims EAH, Krantz KE. Serial studies of renal function during pregnancy and the puerperium in normal women. *J Clin Invest* 1958;37:1764-74.
62. Capeless EL, Clapp JF. When do cardiovascular parameters return to their preconception values? *Am J Obstet Gynecol* 1991;165:883-6.
63. Dam M, Christiansen J, Munck O, Mygind KI. Antiepileptic drugs: Metabolism in pregnancy. *Clin Pharmacokin* 1979;4:53-62.
64. Steen B, Rane A. Clindamycin passage into human milk. *Br J Clin Pharmacol* 1982;13:661-4.
65. Del Priore G, Jackson-Stone M, Shim EK, Garfinkel J, Eichmann MA, Frederiksen MC. A comparison of once-daily and eight hour gentamicin dosing in the treatment of postpartum endometritis. *Obstet Gynecol* 1996;87:994-1000.
66. Kubacka RT, Johnstone HE, Tan HSI, Reeme PD, Myre SA. Intravenous ampicillin pharmacokinetics in the third trimester of pregnancy. *Ther Drug Monit* 1983;5:55-60.
67. Yerby MS, Friel PN, Miller DQ. Carbamazepine protein binding and disposition in pregnancy. *Ther Drug Monit* 1985;7:269-73.
68. Casele HL, Laifer SA, Woelders DA, Venkataramanan R. Changes in the pharmacokinetics of the low-molecular-weight heparin enoxaparin sodium during pregnancy. *Am J Obstet Gynecol* 1999;181:1113-7.
69. Prevost RR, Aki SA, Whybrew WD, Sibai BM. Oral nifedipine pharmacokinetics in pregnancy-induced hypertension. *Pharmacotherapy* 1992;12:174-7.
70. Barton JR, Prevost RR, Wilson DA, Whybrew WD, Sibai BM. Nifedipine pharmacokinetics and pharmacodynamics during the immediate postpartum period in patients with preeclampsia. *Am J Obstet Gynecol* 1991;165:951-4.
71. Kimberlin DF, Weller S, Whitley RJ, Andrews WW, Hauth JC, Lakeman F *et al.* Pharmacokinetics of oral valacyclovir and acyclovir in late pregnancy. *Am J Obstet Gynecol* 1998;179:846-51.
72. CDER. pharmacokinetics in pregnancy — study design, data analysis, and impact on dosing and labeling. Draft guidance for industry. Rockville: FDA; 2004. (Internet at <http://www.fda.gov/cder/guidance/index.htm>.)
73. Nelson MM, Forfar JO. Association between drugs administered during pregnancy and congenital abnormalities of the fetus. *Br Med J* 1971;1:523-7.
74. Bonati M, Bortolus R, Marchetti F, Romero M, Tognoni G. Drug use in pregnancy: An overview of epidemiological (drug utilization) studies. *Eur J Clin Pharmacol* 1990;38:325-8.
75. McBride WG. Thalidomide and congenital abnormalities [letter]. *Lancet* 1961;ii:1358.
76. Lenz W. Kindliche missbildungen nach medikament während der gravidität. *Deutsch Med Wschr* 1961;86:2555-6.
77. Morgan DJ. Drug disposition in mother and foetus. *Clin Exp Pharmacol Physiol* 1997;24:869-73.
78. Martin CB. The anatomy and circulation of the placenta. In: Barnes AC, editor. Intra-uterine development. Philadelphia: Lea & Febiger; 1968. p. 35-67.
79. Higgins CF. ABC transporters: From microorganisms to man. *Annu Rev Cell Biol* 1992;8:67-113.
80. Gottesman MM, Pastan I, Ambudkar SV. P-Glycoprotein and multidrug resistance. *Curr Opin Immunol* 1996;6:610-7.
81. Schinkel AH, Wagenaar E, Mol CAAM, van Deemter L. P-Glycoprotein in the blood-brain barrier

- of mice influences the brain penetration and pharmacological activity of many drugs. *J Clin Invest* 1996;97:2517–24.
82. Mylona P, Glazier JD, Greenwood SL, Slides MK, Sibley CP. Expression of the cystic fibrosis (CF) and multidrug resistance (MDR1) genes during development and differentiation in the human placenta. *Mol Hum Reprod* 1996;2:693–8.
 83. Nakamura Y, Ikeda S, Furukawa T, Sumizawa T, Tani A, Akiyama S, Nagata Y. Function of P-glycoprotein expressed in placenta and mole. *Biochem Biophys Res Commun* 1997;235:849–53.
 84. MacFarland A, Abramovich DR, Ewen SW, and Pearson CK. Stage-specific distribution of P-glycoprotein in first-trimester and full-term human placenta. *Histochem J* 1994;26:417–23.
 85. Allikmets R, Schriml LM, Hutchinson A, Romano-Spica V, Dean M. A human placenta-specific ATP-binding cassette gene (ABCP) on chromosome 4q22 that is involved in multidrug resistance. *Cancer Res* 1998;58:5337–9.
 86. St-Pierre MV, Serrano MA, Macias RIR, Dubs U, Hoehli M, Lauper U, Meier PJ, Marin JJG. Expression of members of the multidrug resistance protein family in human term placenta. *Am J Physiol* 2000;279:R1495–503.
 87. Lankas GR, Wise LD, Cartwright ME, Pippert T, Umbenhauer DR. Placental P-glycoprotein deficiency enhances susceptibility to chemically induced birth defects in mice. *Reprod Toxicol* 1998;12:457–63.
 88. Sugawara I, Kataoka I, Moroshima Y, Hamada H, Tsuruo T, Itoyama S, Mori S. Tissue distribution of P-glycoprotein encoded by a multidrug-resistant gene as revealed by a monoclonal antibody, MRK 16. *Cancer Res* 1988;48:1926–9.
 89. Sugawara I. Expression and function of P-glycoprotein (mdr1 gene product) in normal and malignant tissues. *Acta Pathol Jap* 1990;40:545–53.
 90. Tanabe M, Ieiri I, Nagata N, Inoue K, Ito S, Kanamori Y *et al.* Expression of P-glycoprotein in human placenta: Relation to genetic polymorphism of the multidrug resistance (MDR)-1 gene. *J Pharmacol Exp Ther* 2001;297:1137–43.
 91. Cordon-Cardo C, O'Brien JP, Boccia J, Casals D, Bertino JR, Melamed MR. Expression of the multidrug resistance gene product (P-glycoprotein) in human normal and tumor tissues. *J Histochem Cytochem* 1990;38:1277–87.
 92. Mylona P, Hoyland JA, Sibley CP. Sites of mRNA expression of cystic fibrosis (CF) and multidrug resistance (MDR-1) genes in the human placenta of early pregnancy: No evidence for complementary expression. *Placenta* 1999;20:493–6.
 93. Smit JW, Huisman MT, van Tellingen O, Wilshire HR, Schinkel AH. Absence or pharmacological blocking of placental P-glycoprotein profoundly increased fetal drug exposure. *J Clin Invest* 1999;104:1441–7.
 94. Trezise AE, Romano PR, Gill DR, Hyde SC, Sepulveda FV, Buchwald M, Higgins CF. The multidrug resistance and cystic fibrosis genes have complementary patterns of epithelial expression. *EMBO J* 1992;11:4291–303.
 95. Ushigome F, Takanaga H, Matsua H, Yanai S, Tsukimori K, Nakano H *et al.* Human placental transport of vinblastine, vincristine, digoxin and progesterone: Contribution of P-glycoprotein. *Eur J Pharmacol* 2000;408:1–10.
 96. Pacifici GM, Nottoli R. Placental transfer of drugs administered to the mother. *Clin Pharmacokinet* 1995;28:235–69.
 97. van der Aa EM, Peereboom-Stegeman JHJC, Noordhoek J, Gribnau FWJ, Russel FGM. Mechanisms of drug transfer across the human placenta. *Pharm World Sci* 1998;20:139–48.
 98. Marzolini C, Rudin C, Decosterd LA, Telenti A, Schreyer A, Biollaz J, Buclin T. Swiss mother–child HIV cohort study. Transplacental passage of protease inhibitors at delivery. *AIDS* 2002;16:889–93.
 99. Casey BM, Bawdon RE. Placental transfer of ritonavir with zidovudine in the *ex vivo* placental perfusion model. *Am J Obstet Gynecol* 1998;179:758–61.
 100. Uhr M, Steckler T, Yassouridis A, Holsboer F. Penetration of amitriptyline, but not fluoxetine, into brain is enhanced in mice with blood–brain barrier deficiency due to mdr1a P-glycoprotein gene disruption. *Neuropsychopharmacol* 2000;22:380–7.
 101. Weiss J, Dormann S-MG, Martin-Facklam M, Kerpen CJ, Ketabi-Kiyanvash N, Haefeli WE. Inhibition of P-glycoprotein by newer antidepressants. *J Pharmacol Exp Ther* 2003;305:197–204.
 102. Weiss J, Kerpen CJ, Lindenmaier H, Dormann S-MG, Haefeli WE. Interaction of antiepileptic drugs with human P-glycoprotein *in vitro*. *J Pharmacol Exp Ther* 2003;307:262–7.
 103. Jones KL. Smith's recognizable patterns of human malformation. 5th ed. Philadelphia: WB Saunders; 1997. p. 1–3.
 104. Wilson JG. Current status of teratology — general principles and mechanisms derived from animal studies. In: Wilson JG, Fraser FC, editors. *Handbook of teratology*. vol I. General principles and etiology. New York: Plenum Press; 1977. p 47–74.
 105. Buehler BA, Delimont D, van Waes M, Finnell RH. Prenatal prediction of risk of the fetal hydantoin syndrome. *N Engl J Med* 1990;31:322:1567–72.
 106. Brent RL. Radiation teratogenesis. *Teratology* 1980; 21:281–98.
 107. Shaw GM, Wasserman CR, Lammer EJ, O'Malley CD, Murray JC, Basart AM *et al.* Orofacial clefts, parental cigarette smoking, and transforming growth factor- α gene variants. *Am J Hum Genet* 1996;58:551–61.
 108. Parman T, Wiley MJ, Wells PG. Free radical mediated oxidative DNA damage in the mechanism of thalidomide teratogenicity. *Nat Med* 1999;5:582–5.
 109. Begg EJ, Atkinson HC, Duffull SB. Prospective evaluation of a model for the prediction of milk:plasma drug concentrations from physicochemical characteristics. *Br J Clin Pharmacol* 1992;33:501–5.
 110. Stec GP, Greenberger P, Ruo TI, Henthorn T, Morita Y, Atkinson AJ Jr, Patterson R. Kinetics of theophylline transfer to breast milk. *Clin Pharmacol Ther* 1980; 28:404–8.
 111. Greenberger PA, Odeh YK, Frederiksen MC, Atkinson AJ Jr. Pharmacokinetics of prednisolone transfer to breast milk. *Clin Pharmacol Ther* 1993;53:324–8.

112. Wisner KL, Perel JM, Findling RL. Antidepressant treatment during breast-feeding. *Am J Psychiatry* 1996;153:1132-7.
113. Brixen-Rasmussen L, Halgrener J, Jørgensen A. Amitriptyline and nortriptyline excretion in human breast milk. *Psychopharmacology* 1982;76:94-5.
114. Breyer-Pfaff U, Entenmann A, Gaertner HJ. Secretion of amitriptyline and metabolites into breast milk [letter]. *Am J Psychiatry* 1995;152:812-3.
115. Kemp J, Ilett KF, Booth J, Hackett LP. Excretion of doxepin and *N*-desmethyldoxepin in human milk. *Br J Clin Pharmacol* 1985;20:497-9.
116. Matheson I, Pande H, Alertsen AR. Respiratory depression caused by *N*-desmethyldoxepin in breast milk [letter]. *Lancet* 1985;2:1124.
117. Taddio A, Ito S, Koren G. Excretion of fluoxetine and its metabolite, norfluoxetine, in human breast milk. *J Clin Pharmacol* 1996;36:42-7.
118. Lester BM, Cucca J, Andreaozzi L, Flanagan P, Oh W. Possible association between fluoxetine hydrochloride and colic in an infant. *J Am Acad Child Adolesc Psychiatry* 1993;32:1253-5.
119. Kristensen JH, Ilett KF, Dusci LJ, Hackett LP, Yapp P, Wojnar-Horton RE *et al.* Distribution and excretion of sertraline and *N*-desmethylsertraline in human milk. *Br J Clin Pharmacol* 1998;45:453-7.
120. Ilett KF, Hackett LP, Dusci LJ, Roberts MJ, Kristensen JH, Paech M *et al.* Distribution and excretion of venlafaxine and *O*-desmethylvenlafaxine in human milk. *Br J Clin Pharmacol* 1998;45:459-62.
121. Briggs GG, Samson JH, Ambrose PJ, Schroeder DH. Excretion of bupropion in breast milk. *Ann Pharmacother* 1993;27:431-3.
122. Verbeeck RK, Ross SG, McKenna EA. Excretion of trazodone in breast milk. *Br J Clin Pharmacol* 1986;22:367-70.
123. Wisner KL, Perel JM. Serum nortriptyline levels in nursing mothers and their infants. *Am J Psychiatry* 1991;148:1234-6.